PASS INFORMATION

Title	A national, multicenter, prospective, single-arm registry PASS of pulmonary hypertension patients treated with Riociguat (Adempas®) in China (EXPERT China)
Sponsor	MSD R&D (China) Co., Ltd., a subsidiary of Merck & Co. Inc
Protocol Version identifier	001-01
Date of last version of protocol	13-July-2018
Active substance	Riociguat
Medicinal product(s):	Adempas®
Product reference:	MK-4836 (BAY 63-2521)
Procedure number:	Not Applicable
Marketing authorization holder(s) (MAH)	Bayer AG 51368 Leverkusen, Germany
Joint PASS	Yes
Research question and objectives	The aim of the study is the assessment of the long-term safety profile of riociguat (Adempas®) in real life clinical practice. In addition, it is going to prospectively collect data on clinical effectiveness, resource use, and how Adempas® is used by pulmonary hypertension (PH) experts under real-life conditions.
Country(-ies) of study	China
Author	PPD MSD R&D (China) Co., Ltd.
MAH Contact Person	PPD , Bayer Healthcare Co. Ltd.
Finalization Date	27-Mar-2019

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
AST	Aspartate Transaminase
ARO	Academic Research Organization
BD	Business Day
BNP	Brain Natriuretic Peptide
CD	Calendar Day
cGMP	Cyclic Guanosine Monophosphate
CFR	Code of Federal Regulations
CHD	Congenital Heart Disease
CRF	Case Report Form
CRO	Contract Research Organization
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
DMP	Data Management Plan
EMA	European Medicine Agency
EQ5D	EuroQoL questionnaire
ERA	Endothelin receptor antagonist
FDA	Food and Drug Administration
FPE	First Patient Enrolled
GCP	Good Clinical Practice
GPP	Good Publication Practice
GVP	Good Pharmacovigilance Practice
ICH	International Conference of Harmonization
IEC	Independent Ethics Committee
INN	International Nonproprietary Name
MedDRA	Medical Dictionary for Regulatory Activities
MCV	Mean Corpuscular Volume
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
N/A	Not Applicable
NMPA	National Medical Products Administration
NO	Nitric Oxide
NT-proBNP	N-terminal pro Brain Natiruretic Peptide
WHO functional class	WHO Functional Class
OM	Operating Manual
OS	Observational Study
PAH	Pulmonary Arterial Hypertension
PAS	Post-Authorization Study
PASS	Post-Authorization Safety Study
PEA	Pulmonary Endarterectomy
PH	Pulmonary Hypertension
PSUR	Periodic Safety Update Report
PV	Pharmacovigilance

SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
VAS	Visual Analogue Scale
VKA	Vitamin K Antagonists
6MWT	6-Minute Walk Test

1 RESPONSIBLE PARTIES

Sponsor Contacts	PPD , MSD R&D (China) Co., Ltd.
Investigators	See Site Signature and Responsibilities Log in investigator file at site
Vendor/Collaborator	ARO: GWT-TUD GmbH CRO: Covance Pharmaceutical Research and Development (Beijing) Co. Limited
Shared Responsibilities	
1. Merck/MSD	Clinical director Clinical scientist Clinical operation lead Study statistician Study data manager Study epidemiologist
2. Bayer	Regulatory strategist Study safety lead Qualified person responsible for pharmacovigilance

2 ABSTRACT

Title	**EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension in **China (EXPERT China)**
Protocol Number/ Version	MK-4836-001-01
Date	27-Mar-2019
Author	PPD, MSD R&D (China) Co., Ltd.
Rationale & Background	Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH) are rare and life-threatening diseases. Riociguat (Adempas®) is the first member of a new class of drugs, the sGC-stimulators (soluble guanylate cyclase-stimulators) and the first drug ever having shown efficacy in CTEPH. Riociguat has shown to be effective and well tolerated in patients with PAH and CTEPH randomized controlled trials. It is approved in China to treat patients with Persistent/recurrent after surgical treatment or inoperable CTEPH and patients with PAH. In accordance with the regulatory requirements this registry has been designed to collect information about the long-term safety of Adempas® in real clinical practice outside the regulated environment of a controlled clinical study.
Research Question(s) & Objective(s)	The primary objective is the assessment of long-term safety of Adempas® in real life clinical practice. In addition, it is going to prospectively collect data on clinical effectiveness, resource use, and how Adempas® is used by pulmonary hypertension (PH) experts under real-life conditions.
Study Design	The EXPERT China registry is a national, multicenter, prospective, single-arm study collecting observational data from patients with PAH and CTEPH treated with Adempas®, within the approved indication and providing commercial drug at no cost.
Population	Patients who have been prescribed Adempas® for a medically appropriate use will be eligible to be included into this registry. Indications and contraindications according to the local market authorization should be considered.
Variables	Non-serious adverse event and serious adverse events will be captured, as well as all-cause mortality. Additional information will be provided for the documentation of symptomatic hypotension, hemoptysis and pulmonary hemorrhage as events of special interest. In addition, relevant information on medical

	history, concomitant conditions and medications, resource use and clinical effectiveness will be captured.
Data Sources	The investigator is requested to collect historic data (demographic and clinical characteristics) from medical records, and to collect treatment related data during visits that take place in routine clinical practice.
Study Size	It is planned to enroll 80 patients including a reasonable proportion of patients newly starting Adempas® treatment. Enrollment of patients previously followed in the long-term extension of other riociguat studies is allowed.
Data Analysis	All background variables and outcome parameters will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by summary statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will also be described by absolute value and as change from baseline per analysis time point, if applicable. All analyses will be performed for the total study population (overall analysis) and separately for PH subtypes, patients who newly started or have already been on Adempas® and in patients receiving at least one dose of Adempas®. All statistical details will be described in the Statistical Analysis Plan (SAP). It might have one interim analysis in the middle of the study on primary and secondary endpoints per the need decided by sponsor or authority. A final analysis will be conducted at the end of the study.
Milestones	Start of data collection (First Patient Enrolled, FPE) will be after Adempas® is commercially available in China. The recruitment period will be up to 14 months with an observation period of around 1 year. Data collection will continue until 30 days after the end of Adempas® therapy.

3 AMENDMENTS AND UPDATES

PRIMARY REASON(S) FOR THIS AMENDMENT:

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
PASS INFORMATION	Author MAH Contact Person	PPD, MSD R&D (China) Co., Ltd. PPD, Bayer Healthcare Co. Ltd.	To specify contact persons information
PASS INFORMATION	Marketing authorization holder(s) (MAH)	"Bayer Pharma AG 13342 Berlin, Germany" is updated to "Bayer AG 51368 Leverkusen, Germany".	MAH update was approved in Sep 2018 in China by Bayer.
	LIST of ABBREVIATIONS	Add ALT, AST, BD, CD, FPE, NMPA,OS, PV, VKA Delete BMI, CCB, CFR, GVP, HEOR, ICD, OM, QPPV, WHO DD, WHO FC	Add missing abbreviations, spell out when used for the first time in text, delete abbreviations not applicable in this protocol.
1	RESPONSIBLE PARTIES	Update sponsor name: MSD R&D (China) Co., Ltd., Update the contact information from each party	To update the responsible parties and define sponsorship.
6.1.3	Strengths of study design	"an Adempas® clinical trial" is updated to "two Bayer Phase III clinical trials with riociguat".	To reflect the reality.
6.2.1	Eligibility	"local market authorization" is updated to "local Chinese label for Adempas®"	To emphasize that local Chinese label for Adempas® should be carefully considered by EXPERT China study investigator when assess patient eligibility.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.2.2	Inclusion criterion/criteria	Inclusion criterion bullet 3: WHO Function Class II-III for patients newly treated with Adempas®	Patients have been treated with riociguat either currently in the CHEST and PATENT (riociguat) long term extension trials or started treatment with Adempas® after it was launched in China are different from drug naïve population. Patients under treatment might be on WHO Function Class I which is the result of improvement post-treatment and should be eligible for PASS study.
6.2.3	Exclusion criterion/criteria	Exclusion criterion bullet 1: Add the following: If a patient is currently in the CHEST or PATENT (riociguat) long term extension trials, then the patient can be considered for transition into EXPERT China study after the last dosing of riociguat.	To clarify the exclusion of participants from other interventional studies, except for CHEST or PATENT (riociguat) long term extension trials.
6.2.3	Exclusion criterion/criteria	Add the following two bullet points to the list of exclusion criteria: • Co-administration with specific PDE-5 inhibitors (such as sildenafil, tadalafil or vardenafil) or nonspecific PDE inhibitors (such as dipyridamole or theophylline) (see Section 6.3.16). • Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form (see Section 6.3.16).	To indicate specific PDE-5 inhibitors, non-specific PDE inhibitors and nitric oxide donors are also prohibited medication.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
6.3.16	Prior and concomitant medication	Add a bullet point: Nitrates or nitric oxide donors (physician will be alerted that the combination of PDE5 inhibitors with Adempas® is contraindicated)	Nitric oxide donors are also prohibited medication.
6.7.1	Statistical considerations	It might have one interim analysis in the middle of the study on primary and secondary endpoints per the need decided by sponsor or authority.	To clarify that one interim analysis may be conducted to evaluate safety/ meet agency requirement, which is consistent with Section 2 Abstract.
6.8	Quality Control	"MSD China" is removed	"Sponsor and MSD China" is standard language but not applicable in this study. .Sponsor and MSD China refer to the same legal entity: MSD R&D (China) Co., Ltd.
7.6	Dose Titration	If at any time, the patient has systolic blood pressure lower than 95 mmHg with symptoms and/or signs of hypotension, decrease the dosage by 0.5 mg taken three times a day.	To give a clear definition of "low systolic blood" pressure AND symptoms and/or signs of hypotension. This is consistent with the drug label.
7.7	Dose Interruption	The definition of "Adempas® is interrupted for 3 days or more" is 9 consecutive doses or more.	To clarify the definition and keep consistent understanding and operation at site.
9.2.4	Non-serious Adverse Reaction (NSAR)	An adverse reaction that does not meet any of the serious criteria in Section 9.2.3.	To correct the typographical error indicating the serious criteria source is in Section 10.2.3.

Section Number (s)	Section Title(s)	Description of Change (s)	Rationale
9.2.6	Health Outcome of Interest (HOI)	Not applicable	Health Outcome of Interest that is a standard section but not applicable in this study. This section and corresponding content in Sections 9.1.1 and 9.1.3 is removed.

4 RATIONALE AND BACKGROUND

Pulmonary Arterial Hypertension (PAH) is a rare, progressive and life-threatening disease. It is characterized by a chronic increase in pulmonary vascular resistance (PVR), due to progressive vascular remodeling that can ultimately lead to right heart failure and death [1,2]. Symptoms of PAH are related to right heart failure and include exercise-induced dyspnea, exhaustion, leg edema and decreased quality of life. In untreated patients with idiopathic PAH, the life expectancy is reduced to 2.8 years after diagnosis, whereas in contemporary registries in the era of modern PAH-specific treatments the survival rates have increased to 83% and 58% at 1 and 3 years respectively [3,4]. The incidence is currently estimated as 2.4 cases per million adult inhabitants per year with a prevalence of 15 cases per million adult inhabitants [5]. Available PAH-specific treatments include prostacyclin analogues, endothelin receptor antagonists, and PDE5-inhibitors. The available drugs predominantly act as vasodilators and improve exercise capacity [6]. Despite advances in the clinical management based on these available therapies for PAH, there is still significant unmet medical need for improvement as the mortality of patients with PAH remains high (15% at 1 year and 32% at 3 years) [7].

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is a different progressive and life-threatening type of pulmonary hypertension. Whereas symptoms, as well as epidemiology, of CTEPH are similar compared with PAH, there are significant differences regarding etiology, diagnosis and treatment [8,9]. In CTEPH the increase in pulmonary vascular resistance is a result of a pulmonary artery obstruction by residual organized thrombi [10]. A ventilation-perfusion scan is important for differential diagnosis as a normal scan excludes CTEPH [11]. The standard and potentially curative treatment for CTEPH is pulmonary endarterectomy (PEA). However, 20 to 40% of patients are not eligible for surgery and in 10-15% of patients PH may persist or reoccur after surgery [12-15]. Specific PAH drugs had failed in the past to show efficacy in inoperable CTEPH and before Adempas® no drug treatment has been approved for these patients [16].

Adempas® is the first member of a new class of drugs, the sGC-stimulators (soluble guanylate cyclase-stimulators). It restores the NO-sGC-cGMP pathway and leads to increased generation of cyclic guanosine monophosphate (cGMP) which plays an important role in regulating vascular tone, proliferation, fibrosis, and inflammation. Adempas® directly stimulates sGC independently of nitric oxide (NO), while also increasing the sensitivity of sGC to NO. This appears to be of importance as pulmonary hypertension is associated with pulmonary endothelial dysfunction and can be related to low levels of NO [17-21].

Adempas® is the first drug that could demonstrate robust efficacy in two placebo-controlled, multicenter trials in two different indications of pulmonary hypertension. In the CHEST-1 study, Adempas® showed for the first time robust clinical efficacy in patients with inoperable chronic thromboembolic pulmonary hypertension and in patients with persistent CTEPH after surgery by significantly improving exercise capacity as well as relevant secondary endpoints such as hemodynamics and WHO functional class. In the PATENT-1 study in pulmonary arterial hypertension patients, Adempas® showed significant improvement in exercise capacity in treatment-naïve patients as well as in patients pre-

treated with endothelin receptor antagonists (ERAs) or non-intravenous prostacyclin analogues. At the same time, a consistent significant improvement across the secondary endpoints including hemodynamics, WHO functional class and time to clinical worsening could be demonstrated. In both studies, Adempas® was well tolerated with a good safety profile [22,23].

Adempas was approved in China in Sep 2017. It's approved to treat the patients with the following indications:

Chronic thromboembolic pulmonary hypertension (CTEPH)

For the treatment of adult patients with WHO Functional Class (FC) II to III with persistent/recurrent CTEPH after surgical treatment, or inoperable CTEPH, to improve exercise capacity.

Pulmonary arterial hypertension (PAH)

As monotherapy, or in combination with endothelin receptor antagonists or prostanoid, is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) with WHO Functional Class (FC) II to III to improve exercise capacity. The confirmatory trial enrolled the

PAH population including aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease with WHO-FC II to III.

According to the request from China health authority, the Adempas® registry study is planned. The registry is a multicenter prospective study of patients treated with Adempas® in accordance with the local label. It will capture data from patients with Adempas® treatment in a real-life clinical setting and outside the regulated environment of a controlled clinical study.

The objective of the registry is to describe the safety profile of Adempas® under clinical practice conditions. In addition, the registry offers a structured prospective collection of data on the clinical effect, patient-reported outcomes and resource use and to gather information on how Adempas® is used by PH experts.

In agreement with EMA, EXPERT, a global, multicenter, prospective, uncontrolled, non-interventional cohort registry of patients treated with commercial riociguat, designed to collect information about the long-term safety of Adempas® in real clinical practice outside the regulated environment of a controlled clinical study, was implemented. The proposed China registry is based on the EXPERT study considering local regulatory requirements. Also considering the difficulty of local patients' affordability sponsor will provide Adempas with no charge. However, it won't change the nature of observational data in the medical practice.

5 RESEACH QUESTION AND OBJECTIVES

5.1 Primary Objective

The primary objective is the assessment of long-term safety of Adempas® in real life clinical practice.

5.2 Secondary Objective(s)

The secondary objectives in this study are:

- Long-term safety of Adempas® in the different PH indications (PAH, CTEPH)
- Effectiveness of Adempas® in the long-term follow-up of PH patients
- Information on resource use
- Information on how Adempas® is used (e.g. indication and indication subgroups, dose)

6 RESEARCH METHODS

6.1 Study Design

This registry is a national, multicenter, prospective, single-arm study of patients who will be treated with commercial riociguat for the locally approved indications of PH. The study will start after Adempas® has been authorized and made commercially available in China.

All patients prescribed with Adempas® for a medically appropriate use, consent to participate, and fulfill the selection criteria are eligible for enrollment into the study. Once enrolled, all aspects of the study will be conducted in an observational manner with no additional visits, procedures, etc. required as part of the study. All decisions on clinical management of the patient, including the actual treatment duration will be determined solely by the physician.

Patients will be followed up for an observation period of at least 1 year or until 30 days after end of Adempas® therapy. The enrollment period to obtain the required 80 patients is expected to be up to 14 months. Patient's clinical information will be documented at time of the initial visit and approximately every three to six months according to routine clinical practice thereafter. Data collection will continue until 30 days after the end of Adempas® therapy. Serious adverse events will be followed up until resolution.

Considering the difficulty of affordability of local patients during the study, sponsor will provide drug with no charge once medical decision on the prescription is made by physician and patients signed the informed consent. The free drug will be provided from the date of the first patient in to one year after the last patient in.

6.1.1 Primary Endpoint(s)

The primary endpoints are:

- Incidence of adverse events/serious adverse events
- Incidence of all-cause mortality

6.1.2 Secondary Endpoint(s)

The secondary endpoints are:

Safety

- Incidence of AE (Adverse Event) and SAE (Serious Adverse Event) in the different PH indications (PAH, CTEPH)
- Incidence of AE of interest overall and in the different PH indications (PAH, CTEPH)

Effectiveness

- Clinical effect in the follow-up of PH patients as compared with baseline, if both baseline and post baseline measurements are available
  - 6-minute walk test
  - WHO FC
  - Borg dyspnoea index
  - Biomarkers (BNP, NT-pro BNP)
  - EQ5D VAS
  - Haemodynamic parameters from right heart catheter measurement

Resource use

- Hospitalization/ outpatient visits
- Administration and any change in drug treatment for PAH or CTEPH

6.1.3 Strengths of Study Design

In this therapeutic area a multicenter exposure registry with a mix of patients previously enrolled in two Bayer Phase III clinical trials with riociguat and patients newly starting Adempas® allows for a structured prospective documentation of long-term data on safety, clinical effect, and information on how Adempas® is used by PH experts. As Adempas® is the first sGC-stimulator in clinical use and all available clinical data in Chinese patients derive from well-defined clinical studies, this registry may collect additional data on important potential safety risks, drug interactions and missing information.

6.2 Setting

6.2.1 Eligibility

Patients who have been prescribed Adempas® for a medically appropriate use will be eligible to be included into this registry. Indications and contraindications according to the local Chinese label for Adempas® should be carefully considered.

6.2.2 Inclusion Criterion/Criteria

- Patients who have been diagnosed with PAH or CTEPH
- Female and male patients who start or are on treatment with Adempas®
- WHO Function Class II-III for patients newly treated with Adempas®
- Written informed consent

6.2.3 Exclusion Criterion/Criteria

- Patients currently participating in an interventional clinical trial (If a patient is currently in the CHEST or PATENT (riociguat) long term extension trials, then the patient can be considered for transition into EXPERT China study after the last dosing of riociguat.)
- Female patient who is pregnant
- Patients with severe hepatic impairment (Child Pugh grade C)
- Patients with SBP<95 mmHg when newly treated with Adempas®
- Patients who have been diagnosed with idiopathic interstitial pneumonia
- Co-administration with specific PDE 5 inhibitors (such as sildenafil, tadalafil or vardenafil) or nonspecific PDE 5 inhibitors (such as dipyridamole or theophylline) (see Section 6.3.16).
- Co-administration with nitrates or nitric oxide donors (such as amyl nitrite) in any form (see Section 6.3.16).
- Any condition which, in the opinion of the investigator may confound the results or result in unwarranted risk in administering Adempas® to the patient.

6.2.4 Discontinuation of Adempas® Treatment

If the patient discontinues Adempas® during the study, the reason for discontinuation will be recorded. Patients should discontinue Adempas® treatment if any of the following occur:

- Adverse event(s) where the investigator believes discontinuation of treatment with Adempas® is in the best interest of the patient
- Pregnancy

- Any other reason, that in the opinion of the investigator precludes further treatment with Adempas®.

After discontinuation of treatment with Adempas®, the follow-up documentation will continue until 30 days after end of therapy.

6.2.5 Withdrawal From the Study

Each patient has the right to refuse further participation in the study at any time and without providing any reasons. A patient's participation is to be terminated immediately upon his/her request. The investigator should seek to obtain the reason and record this on the Case Report Form (CRF). Patients should also be withdrawn from the study for any other reason, that in the opinion of the investigator precludes further participation by the patient.

In this study, withdrawal from the study is independent of the underlying therapy. On the other hand, the follow-up documentation will continue until 30 days after end of therapy.

6.2.6 Replacement

Patients will not be replaced after drop out.

6.2.7 Representativeness

Source population of the present study is patients with PH, specifically PAH and CTEPH. Patients with this rare condition are mostly diagnosed and managed in specialized centers. This includes the initiation and any change of specific drug therapy. The participation of these specialized centers into the registry, the consecutive recruiting of patients and the broad definition of selection criteria is going to ensure the representativeness of the study population.

6.2.8 Visits

The study protocol does not define exact timing of the follow-up visits. The clinical information will be collected, if available and done as per standard of care.

The investigator will document an initial visit, follow-up visits and a final visit for each patient in the case report form (CRF). Follow-up visits in clinical practice usually take place every 3 to 6 months. The CRF will allow for the documentation of visits as performed according to the management of the individual patient.

The final visit is meant to document the end of observation.

Patients will be followed up for an observation period for around 1 year or until end of study (until the last subject has been followed for 1 year) or until 30 days after end of Adempas® treatment. The enrollment period to obtain the required 80 patients is expected to be up to 14 months, therefore the study period from FPE to LPLV will be ~26 months.

Enrollment/Initial Visit

Once a patient is found eligible for inclusion, the investigator will inform the patient about the study. This will include discussing the consent form and asking the patient to read and – when agreeing to participate – sign the informed consent.

For patients in Bayer studies PATENT 2 and CHEST 2, their eligibility for EXPERT-China study will be evaluated after the completion of the Termination Visit and the Safety Follow-up Visit 30 days later in BAY 11349/12935.

The following information will be collected (details in Section 6.3):

- Patient demographics
- Medical history
- Comorbidity
- Adverse events
- PH etiology according to Nice Classification 2013 and disease history
- Pregnancy status
- History of smoking
- 6-minute walking distance*
- WHO FC*
- Borg dyspnea index*
- EQ5D VAS*
- Lung function*, Cardiac rhythm
- Hemodynamic parameters from right heart catheter measurement*
- Biomarkers (NT-proBNP, BNP) *
- Laboratory tests*
- Systemic BP before start of Adempas®
- Treatment:
  - Relevant prior and concomitant medication
  - PAH-specific drugs or Adempas®
- Resource use

*if available and done as per standard of care

Follow-up Visits During Treatment

Follow-up examinations in clinical routine usually take place every 3 to 6 months. The CRF will allow for visits to be documented according to the management of the individual patient. At each of these visits the following will be documented:

- Adverse events
- Changes of treatment
- Changes regarding demographics, pregnancy, smoking
- 6-minute walking distance*
- WHO FC*
- Borg dyspnea index*
- EQ5D VAS*
- Lung function*, Cardiac rhythm,
- Hemodynamic parameters from right heart catheter measurement *
- Biomarkers (NT-proBNP, BNP) *
- Laboratory tests*
- Resource use

*if available and done as per standard of care

Final Visit and End of Observation Period

The final data collection (last visit) is 30 days after discontinuation of therapy or at end of study (whichever is earlier). At this final observation point, the patient's condition and a treatment assessment will be documented as at the follow-up visits with additional information on:

- Regular end of observation, or
- Discontinuation of therapy /Withdrawal from study
- Reason for discontinuation/withdrawal, i.e.: patient failed to follow up, patient decision, investigator decision, pregnancy, insufficient/no treatment effect, unexpected strong treatment effect, (suspected) drug interaction, SAE (must be reported **immediately**), death (date and relation to disease or treatment), therapy change (which therapy and reason for switch), center closed, study termination

6.3 Variables

The investigator collects historic data (demographic and clinical characteristics) from medical records if available, or else by interviewing the patient. Likewise, the investigator collects treatment related data during the initial visit and follow-up visits based on assessments that are performed routinely. The investigator documents the study-relevant data for each patient in the case report form (CRF).

Table 1 Tabulated overview on variables collected during the study

Variables	Initial visit	Follow-up visit(s)	Final visit
Demographics	X	X	X
Medical history	X		
Concomitant disease	X	X	X
Adverse Events**	X	X	X
PH etiology	X		
Pregnancy status	X	X	X
Smoking history/status	X	X	X
Systemic BP before start of Adempas®	X		
6-minute walk test*	X	X	X
WHO FC*	X	X	X
Borg dyspnea index*	X	X	X
EQ5D VAS*	X	X	X
Hemodynamic measurements, lung function, cardiac rhythm*	X	X	X
Biomarkers*	X	X	X
Laboratory tests*	X	X	X
Treatment medication	X	X	X
Concomitant medication	X	X	X
Resource use in hospital and outpatient care	X	X	X

* If data available and done as per standard of care

**Serious Adverse Events must be reported to Bayer within 24 hours.

6.3.1 Variables to Determine the Primary Endpoint(s)

The variables for primary objective are:

- Adverse events (AE) and serious adverse events (SAE)
- All-cause mortality

6.3.2 Variables to Determine the Secondary Endpoints

The outcome variables for secondary objectives are:

- AE and SAE in the different PH indications (PAH, CTEPH)
- Adverse events of interest
  - o Symptomatic Hypotension (date BP measurement, symptoms)
  - o Haemoptysis and pulmonary haemorrhage (serious and non-serious).

  Specific information regarding relevant history, current condition, diagnostics, treatment, specific lab values and outcome to be documented in a specific CRF section in case AE/SAE of interest occurred
- Measurements of clinical effect
  - o 6-minute walk test
  - o WHO FC
  - o Borg dyspnoea index
  - o EQ5D VAS
  - o Haemodynamic parameters from right heart catheter measurement
  - o Biomarkers
- Resource use
  - o Hospitalization (due to PH or other reason, emergency admission, intensive care unit, number of days)
  - o Outpatient visits at PH centre
  - o Home care (nurse, days per week, hours per day)
  - o Drug use, including switch or interruption or discontinuation of Adempas® and associated reason

6.3.3 Demographics

For demographic/socio-demographic assessment, the following data will be recorded:

- Year of birth
- Sex

- Height and Weight

6.3.4 Co-morbidities (medical history, concomitant diseases)

Co-morbidities are any medical findings, whether they pertain to the study indication, that were present before start of therapy with Adempas®, independent of whether they are still present.

Findings meeting the criteria listed below are relevant to the study indication and should be documented if collected as part of routine clinical practice:

- Date of first PH diagnosis (month/year)
- Aetiology of PH according to Nice Classification 2013, subgroups of CTEPH (inoperable, post-surgery), subgroups of PAH (monotherapy, combination therapy)
- Relevant concomitant diseases (e.g. vascular disease, diabetes, cancer)
  - Date of diagnosis
- History of haemoptysis (date frequency, severity, bronchial arterial embolization (BAE), other pulmonary disease, trauma)
- Hepatic impairment (no/yes)
  - Child-Pugh classification
- Renal impairment (no/yes)
  - Severity
  - Estimated Glomerular filtration rate by Cockroft-Gault formula

For any comorbidity, the specific diagnosis as well as start and stop dates/ongoing must be documented.

6.3.5 Pregnancy

- Pregnancy Monitoring Form

6.3.6 Smoking

- Smoking history
- Current status

6.3.7 6-minute Walk Test (if available)

- Date
- Distance

6.3.8 WHO Functional Class (if available)

- Date
- Result

6.3.9 Borg Dyspnoea Index (if available)

- Date
- Result

6.3.10 EQ5D Visual Analog Scale (if available)

- Date
- Score

6.3.11 Haemodynamic Measurements (if available)

- Date
- Mean pulmonary arterial pressure (mPAP, mmHg)
- Pulmonary vascular resistance (dyn*sec*cm^{-5})
- Pulmonary capillary wedge pressure (PCWP, mmHg)
- Right atrial pressure (RAP, mmHg)
- Cardiac index (L/min/m^2)

6.3.12 Cardiac Rhythm (if available)

- Date
- Normal sinus rhythm, atrial fibrillation, atrial flutter or other arrhythmia

6.3.13 Lung Function (if available)

- Date
- TLC, FVC, FEV1, DLCO, PaO_2, $PaCO_2$, O_2 BGA

6.3.14 Biomarkers (if available)

- Date
- Brain Natriuretic Peptide (BNP; pg/mg or pmol/l)
- NT-pro BNP (N-terminal pro Brain Natiruretic Peptide, pg/mg or pmol/l)

6.3.15 Laboratory Tests (if available)

- Date

- Haemoglobin
- Haematocrit
- INR (if on VKA treatment)
- Creatinine
- Transaminases (ALT/AST)

Additional laboratory tests for CHD patients only

- Date
- Uric acid
- Sodium
- Iron, Ferritin, Transferrin, Soluble transferrin receptor, sTfR-ferritin index
- C-reactive protein
- MCV, MCH, MCHC
- Homocysteine

6.3.16 Prior and Concomitant Medication

All medication taken before study start (initiated and stopped before study start) is termed prior medication. All medication taken in addition (either initiated before study start or during the study) is termed concomitant medication.

Prior and concomitant medication meeting the criteria listed below are considered to be relevant and must be documented:

- PH/PAH-specific therapy
  - Adempas®
  - ERA
    - Bosentan
    - Ambrisentan
  - PDE-5 inhibitors (physician will be alerted that the combination of PDE5 inhibitors with Adempas® is contraindicated)
  - Nitrates or nitric oxide donors (physician will be alerted that the combination of PDE5 inhibitors with Adempas® is contraindicated)
  - Prostacyclins
    - Epoprostenol
    - Treprostinil
    - Iloprost

        - Beraprost
    - Other specific targeted therapy: calcium channel blocker
    - Oral anticoagulation
        - Vitamin K antagonists
        - Other
- Other medications (only CHD: other cardiovascular drugs, antiplatelets)

Information to be documented includes:

- Trade name and INN
- Start and stop date
- Date of dose change, switch or addition of a specific drug/Adempas®
- Reason for change (lack of efficacy or tolerability, patient's request, administrative)
- Dose
- Unit
- Frequency
- Administration mode
- Indication

Additional information on Adempas® to be documented includes:

- Individual dose after initial dose adjustment period
- BP before the 1st administration

6.4 Data Sources

The investigator collects current and historic patient data (demographic and clinical characteristics) from medical records if available. Likewise, the investigator collects treatment related data during visits that take place in routine practice. Each patient is identified by a unique central patient identification code, which is only used for study purposes. For the duration of the study and afterwards, only the patient's investigator is able to identify the patient based on the patient identification code.

6.5 Study Size

Per regulatory commitment, study accrual will continue until at least 80 patients are enrolled, including a reasonable number of newly treated Adempas® patients. The study will allow to prospectively collect data on the safety and clinical effect of Adempas® treatment in real-life clinical practice in China.

The sample size rationale is listed below.

- Epidemiology of PH indicates a low incidence (incidence of PAH: 2-8/million/y; incidence of CTEPH in Great Britain: 12.3-16.6/million/y; no incidence data available in China).
- Enrolment period: The enrollment period available for this study is limited to <1.5 years because commercial drug will not be available for 1 year after approval, patients will be observed for around 1 year, and time is needed for data clean-up and analysis to complete/submit the study report with the renewal submission ~12 months prior to license expiry".
- Limited number of PH centres (approximately 10 active PH centres) in China.
- Therapeutic environment: Adempas® is not the only option for PAH treatment.
- Chinese patient number enrolled in the CTEPH and PAH pivotal studies (109 patients were enrolled in over 2 years; this corresponds to 81 patients in 1.5 years).

6.6 Data Management

An Academic Research Organization (ARO) will be selected and assigned for EDC system development. The CRF will be part of the EDC system which allows documentation of all outcome variables and covariates by all participating sites in a standardized way. Information on the EDC system will be available upon request. Detailed information on data management, including procedures for data collection, retrieval and preparation will be provided in the Data Management Plan (DMP), which will be available upon request.

For information on quality control, refer to Section 6.7.7.

6.7 Data Analysis

6.7.1 Statistical Considerations

Statistical analyses of this study will be descriptive.

All background variables and outcome parameters will be analyzed descriptively with appropriate statistical methods: categorical variables by frequency tables (absolute and relative frequencies) and continuous variables by summary statistics (i.e. mean, standard deviation, minimum, median, quartiles and maximum). Continuous variables will also be described by absolute value and as change from baseline per analysis time point, if applicable.

All analyses will be performed for the total study population (overall analysis) and separately for PH subtype and relevant subgroups, (e.g., age, gender, incident and prevalent patients, functional class at baseline, titrated dose), if patient numbers are sufficient. Prevalent patients are here defined as patients already on treatment when enrolled in the study, whereas incident patients will be patients newly starting Adempas®.

Patients receiving at least one dose of Adempas® will be included in the analysis. Whenever reasonable, data will be stratified by subgroups (e.g. age, gender).

All therapies documented will be coded using the World Health Organization – Drug Dictionary (WHO-DD). Medical history, any diseases and AEs will be coded using the latest Medical Dictionary for Regulatory Activities (MedDRA) version.

All statistical details including calculated variables and proposed format and content of tables will be detailed in the Statistical Analysis Plan (SAP). The SAP will be finalized before study database lock. The SAP will be available upon request.

It might have one interim analysis in the middle of the study on primary and secondary endpoints per the need decided by sponsor or authority. The proportion of incident and prevalent subjects will be tracked. The final analysis will be performed after end of the study which is the date the analytical dataset is completely available.

All background data such as patient demographics, PH group and indication-specific characteristics and prior or concomitant medication of PH, and concomitant diseases will be described by presenting frequency distributions and/or basic summary statistics.

Sample size and disposition information by analysis time point will be displayed in a frequency table.

6.7.2 Analysis of Treatment Data

Duration and dose of the Adempas® treatment during the observation period will be calculated for each patient. The dose will be displayed at the different visits/time windows. The number of patients adding and removing various PH medications (including Adempas®) will be summarized using frequency tables.

6.7.3 Analysis of Primary Outcome(s)

The main goal of this national registry is to assess the long-term safety of Adempas® in real life clinical use. Incidences of treatment-emergent adverse events, serious adverse events and all-cause mortality will be calculated, including adverse events of interest. An adverse event is considered as treatment-emergent when it has started or worsened after first dose of study medication after enrollment up to 2 days after end of treatment with study medication.

For the events, the ‘raw’ incidence proportion (regardless of the time each patient is treated), i.e. number of patients with events divided by the number of treated patients, will be presented as well as incidence rates, i.e. number of patients with events divided by the cumulative person-time on treatment (person-years) separately for incident and prevalent patients.

If the patient numbers allow, the statistics will be calculated for Adempas® and stratified for medically relevant subgroups, e.g.:

- Age
- Gender

- Aetiology (Nice Classification of PH)
- Hepatic impairment at baseline
- Renal impairment at baseline
- WHO functional class group at baseline
- According to e.g. 6 MWD thresholds ≥380 m versus < 380 m at baseline
- Type of PH pre-treatment
- Concomitant medication use
- Systolic blood pressure at baseline
- Dosing level

A comprehensive list of medically relevant subgroups will be added to the SAP.

Tables which show the incidence proportion of adverse events overall and by MedDRA preferred term within the primary SOC will also be presented. Incidences of adverse events and serious adverse events starting more than 2 days after end of treatment will be tabulated separately.

6.7.4 Analysis of Secondary Outcome(s)

The secondary safety outcomes will be analyzed similar to the primary outcomes. Subgroup analyses will be conducted for selected secondary endpoints (e.g. 6-minute walk test, WHO FC, hospitalization).

Analyses of adverse events will be conducted for PH subgroups (e.g., inoperable vs. post-surgery CTEPH patients, monotherapy vs. combination therapy PAH patients).

For the effectiveness variables, summary statistics and changes form baseline will be calculated for

- 6-minute walking test
- Borg dyspnea index
- EQ5D VAS
- Hemodynamic measurements
- Biomarkers

WHO FC will be analyzed by frequency tables including changes from baseline.

The variables of hospitalization due to PH and drug utilization (reason for drug switch or interruption or discontinuation of Adempas®) will be analyzed by frequency tables and summary statistics.

6.7.5 Analysis of Safety Data

Other safety outcomes, e.g. laboratory values, cardiac rhythm, and lung function, will be analyzed by frequency tables or summary statistics and changes from baseline.

6.7.6 Bias, Confounding and Effect-Modifying Factors

While study drug will be provided, the data collection is being based on real life clinical practice, including timing of visits, treatment, and evaluation. There are several potential sources of bias including missing data, misclassification, recall bias, reporting bias, survivor bias, as well as selection biases. To reduce patient selection bias physicians must document that they have tried to recruit consecutive eligible patients who receive Adempas®.

To decrease the reporting bias, 100% source data verification will be performed on critical study data. Detailed information will be described in site monitoring plan (SMP). For survivor bias, see Section 6.9.

Baseline characteristics of the patients will be examined and described in detail.

6.7.7 Quality Review

One hundred percent source document verification will be conducted on critical study data. The purpose is to review the documented data for completeness and plausibility, adherence to the study protocol and verification with source documents. To accomplish this, monitors will access medical records on site for data verification. Detailed measures for quality reviews will be described in the SMP. The SMP will be available upon request.

6.7.8 Storage of Records and Archiving

The sponsor will make sure that all relevant documents of this study including CRFs and other patient records will be stored after end or discontinuation of the study at least for 15 years. Other instructions for storage of medical records will remain unaffected.

The investigators participating in the study must archive documents at their sites according to local requirements, considering possible audits and inspections from the sponsor and/or local authorities. It is recommended to store documents for a retention period of at least 15 years.

6.7.9 Certification/Qualification of External Parties

N/A.

6.8 Quality Control

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted

and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Clinical and Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

Before study start at the sites, all investigators will be sufficiently trained on the background and objectives of the study and ethical as well as regulatory obligations. Investigators will have the chance to discuss and develop a common understanding of the study protocol and the CRF.

An ARO (Academic Research Organization) will be selected and assigned for EDC system development, quality control, verification of the data collection, data analysis and data transfer to the sponsor.

All outcome variables and covariates will be recorded in a standardized CRF. After data entry, missing or implausible data will be queried, and the data will be validated. A check for multiple documented patients will be done.

Detailed information on checks for completeness, accuracy, plausibility and validity are given in the Data Management Plan (DMP). The same plan will specify measures for handling of missing data and permissible clarifications. The DMP is available upon request.

Electronic records used for capturing patient documentation (eCRF) will be validated. The documentation is available upon request.

6.9 Limitations of the Research Methods

Typical limitations inherent to the study design of registries have recently been summarized in a state-of-art paper based on discussions at the 5th World Symposium on PH in Nice [24], with a focus on survival, various types of bias, and missing data.

The large majority of patients to be included will be prevalent cases of PAH/CTEPH. In the French PAH registry it could be shown that survival in PAH cohorts is not only strongly influenced by clinical baseline characteristics and associated conditions (e.g. systemic sclerosis, HIV infection) but also by the time-interval between diagnosis and recruitment into the registry (survivor bias). Patients entering such a registry as prevalent case may be more likely to have relatively stable disease and/or better response to PAH management compared to patients not included [25].

With regard to safety results, such as frequency and kind of adverse reactions, it will be impossible to compare the results under Adempas® treatment with those on other therapies, as we have only comprehensive AE/SAE information available for Adempas® treated patients.

Small sample size is another limitation of the study due to restricting circumstances.

7 STUDY INTERVENTION

Study intervention is defined as marketed Adempas® provided by Sponsor to investigator intended to be administered to a study participant according to the study protocol.

Clinical supplies will be packaged to support enrollment. Clinical supplies will be affixed with a clinical label in accordance with regulatory requirements.

7.1 Study Interventions Administered

The study interventions to be used in this study are outlined below in Table 2.

Table 2 Study Interventions

Intervention Name	Regimen/Treatment Period	Unit Dose Strength	Dose Formulation	Route of Administration	Sourcing
Adempas®	1.0 mg Tid	1.0 mg	Tablet	Oral	Central
Adempas®	1.5 mg Tid	0.5 mg+ 1.0 mg	Tablet	Oral	Central
Adempas®	2.0 mg Tid	1.0 mg+ 1.0 mg	Tablet	Oral	Central
Adempas®	2.5 mg Tid	2.5 mg	Tablet	Oral	Central

All supplies indicated in Table 2 will be provided per the 'Sourcing' column. The study site is responsible for recording the lot number, manufacturer, and expiry date for investigational product (if applicable) as per local guidelines.

Refer to Section 7.1 for details regarding administration of the study intervention.

7.2 Preparation/Handling/Storage/Accountability

7.2.1 Dose Preparation

The doses to be used in this study is based on the label (Dosage and Administration) and physician's judgement.

7.2.2 Handling, Storage, and Accountability

The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.

Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.

The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (i.e., receipt, reconciliation, and final disposition records).

For all study sites, the local country Sponsor personnel or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.

The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed by the Sponsor.

The investigator shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

7.3 Measures to Minimize Bias: Randomization and Blinding

7.3.1 Intervention Assignment

Participants in this study will all receive Adempas®.

7.3.2 Stratification

No stratification based on age, sex or other characteristics will be used in this study.

7.3.3 Blinding

This is an open-label study. Therefore, the Sponsor, investigator, and participant will know the intervention is administered.

7.4 Study Intervention Compliance

The intervention is used in real clinical practice. There is no specified compliance required in the protocol.

7.5 Concomitant therapy

Medication specifically prohibited in the label are not allowed.

7.5.1 Rescue Medications and Supportive Care

No rescue or supportive medications are specified to be used in this study.

7.6 Dose Titration

The recommended starting dosage is 1 mg taken 3 times a day. For patients who may not tolerate the hypotensive effect of Adempas®, consider a starting dose of 0.5 mg taken three times a day. If systolic blood pressure remains greater than 95 mmHg and the patient has no signs or symptoms of hypotension, up-titrate the dose by 0.5 mg taken three times a day. Dose increases should be no sooner than 2 weeks apart. The dose can be increased to the highest tolerated dosage, up to a maximum of 2.5 mg taken three times a day. If at any time, the patient has systolic blood pressure lower than 95 mmHg with symptoms and/or signs of hypotension, decrease the dosage by 0.5 mg taken three times a day.

7.7 Dose Interruption

If a dose is missed, advise patients to continue with the next regularly scheduled dose.

In case Adempas® is interrupted for 3 days (9 consecutive doses) or more, re-titrate Adempas®.

7.8 Intervention After the End of the Study

There is no study-specified intervention following the end of the study.

7.9 Clinical Supplies Disclosure

This study is open-label; therefore, the participants, the study site personnel, the Sponsor, and/or designee are not blinded. Study intervention (name, strength, or potency) is included in the label text; random code/disclosure envelops, or lists are not provided.

8 PROTECTION OF HUMAN SUBJECTS

8.1 Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Specifics about a study and the study population will be added to the consent form template.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

8.2 Ethical Conduct of the Study

In this study, Adempas® is prescribed in the customary manner in accordance with the terms of the marketing authorization. The treatment decision falls within current practice and the prescription of the medicines is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring process is required for participation or during the study. Epidemiological methods will be used for the analysis of the collected data.

8.3 Regulatory Authority Approvals/Authorizations

The study will be carried out within an approved indication in accordance with guidelines and regulations of NMPA (National Medical Products Administration) and applicable local law(s) and regulation(s). ICH-GCP guidelines and China GCP will be followed whenever possible.

Documented approval from appropriate IECs will be obtained for all participating centers prior to study start. When necessary, an extension, amendment or renewal of the IECs approval must be obtained and also forwarded to the sponsor. The IECs must supply to the sponsor, upon request, a list of the IECs members involved in the vote and a statement to confirm that the IECs is organized and operates according to applicable laws and regulations.

8.4 Confidentiality

The sponsor as well as all investigators ensure adherence to applicable data privacy protection regulation. Data are transferred in encoded form only. The entire documentation made available to the sponsor does not contain any data which, on its own account or in conjunction with other freely available data, can be used to re-identify natural persons. The investigators are obligated to ensure that no documents contain such data.

All records identifying the subject will be kept confidential and will not be made publicly available. Patient names will not be supplied to the sponsor. If the patient name appears on any document, it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws.

The investigator will maintain a list to enable patients' records to be identified in case of queries. In case of a report of a serious adverse event (SAE), the responsible pharmacovigilance person may ask for additional clarification. In that case, the company is not allowed to directly contact the patient. All additional information will be provided by the investigator.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1 Adverse Event Reporting

9.1.1 Investigator Responsibility

If the investigator becomes aware of any serious adverse event (SAE), including death due to any cause, or non-serious adverse reaction (NSAR) following the use of Adempas®, the event must be reported according to Table 3. The investigator must evaluate each AE for causality and record causality on the AE form for each event reported.

Investigator should follow CRF/EDC completion guidance to collect AE occurred during the study.

Investigator should also follow China related regulations to report SAE and NSAR to China agency.

9.1.2 Management and Reporting

The documentation of any AE/SAE starts from the inform consent form signing and ends with the completion of the observation period of the patient. However, any AE/SAE occurring up to 30 days after the last intake of Adempas® has to be documented, even if this period goes beyond the end of the observation period.

Non-serious AEs

All adverse events (AE) must be documented in the CRF/EDC system following the CRF/EDC completion guidance. For each AE, the investigator must assess and document the seriousness, duration, relationship to study drug, action taken and outcome of the event.

The outcome of all reported AEs (resolution, death etc.) will be followed up and documented. Where required, investigators might be contacted directly by the responsible person from CRO to provide further information.

Non-serious ARs

All non-serious ARs occurring under treatment with Adempas® that qualify for expedited reporting will be submitted to the relevant authorities according to national regulations by Bayer China; however, all investigators must obey local legal requirements.

For non-serious ARs occurring under non-Merck drugs the investigator has to account for and comply with the reporting system of the product’s Marketing Authorization Holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

For NSAR, investigator enters information in CRF/EDC system within 7 CD (Calendar Days) of event awareness, and ARO sends NSAR in linelisting to Bayer China PV (Pharmacovigilance) once a week (Table 3).

Serious Adverse Event(SAE)

Upon notification of SAE, investigator completes Bayer Observational Study (OS) Adverse Event Form and forwards the form to CRO (Contract Research Organization) within 24 hours of event awareness. CRO forwards the SAE to Bayer China PV within 1 BD (Business Days)/3 CD from time of receipt from investigator. The outcome of all reported SAEs (resolution, death etc.) will be followed up and documented by investigator. Where required, investigators might be contacted directly by the responsible person from CRO to provide further information.

Submission to the relevant authorities according to national regulations will be done by Bayer China for SAEs occurring under Adempas® treatment; however, all investigators must obey local legal requirements.

For any serious drug-related AE occurring after study end, the standard procedures that are in place for spontaneous reporting must be followed.

For SAEs that occurred while administering non-Merck drugs the investigator must account for and comply with the reporting system of the product's marketing authorization holder within the frame of local laws and regulations as well as other locally applicable laws and regulations.

AE of Special Situations

Any AE of special situations will be captured in CRF/EDC system by investigator following the CRF/EDC completion guideline.

Pregnancy

If a pregnancy occurs during the study, although it is not a serious adverse event, it should be reported within the same time limits as a serious adverse event. The outcome of a pregnancy should be followed up carefully and any abnormal result of the mother or baby should be reported.

Upon notification of pregnancy, investigator should complete Pregnancy Monitoring Form and forward it to CRO within 24 hours of event awareness. CRO forwards the Pregnancy Monitoring_Form to Bayer China_PV_within 1 BD/3 CD from time of receipt from investigator.

9.1.3 Evaluation

Bayer will be responsible for safety information evaluation as MAH (Marketing Authorization Holder) of Adempas®.

Whenever new important safety information is received, e.g. case reports from an investigator, the reports are processed and entered into the global pharmacovigilance safety database. These reports will be reviewed on a regular basis (for information on collection, management and reporting of case reports, refer to Section 9.1.2 and 9.1.3). If a potential safety signal is suspected, an investigation of the suspected potential signal will be performed according to internal standard operating procedures, for further evaluation within the context of benefit risk.

Table 3 AE Reporting Timeframes and Process for Investigators and Vendors

EVENT TYPE	INVESTIGATOR TIMEFRAME Investigator to Vendor	VENDOR TIMEFRAME Vendor to Bayer
SAE, regardless of causality (primary data collection) Serious Special Situation, regardless of causality Pregnancy	CRO:24 hours from receipt	CRO: 1 BD/3 CD from time of receipt from investigator
NSAR	ARO: 7 CD from receipt	ARO extracts (as line listing) the non-serious ARs from the study database and send the line listing to Bayer PV department every week
Note: Spontaneously reported adverse events for other Merck products: If investigator elects to submit AEs for other Merck product, they should complete AE Intake Form and fax the form to MSD China PV team PPD within 10 calendar days of event awareness. Follow-up to any event-submit using above timeframes BD-Business Day; CD-Calendar Day		

9.1.4 Study Report

The final study report, and any planned interim analysis, will include aggregate listings of all events collected for Adempas® and will be provided to regulatory agencies by the sponsor as required.

9.1.5 Periodic Safety Update Reports:

Any relevant safety information will be summarized in the appropriate Periodic Safety Update Report (PSUR)/ Periodic Benefit Risk Evaluation Report (PBRER) and/or Development Safety Update Reports (DSUR) if required.

9.2 Definitions

9.2.1 Adverse Event (AE)

Any untoward medical occurrence in a patient or clinical investigation subject administered sponsor's product and which does not necessarily have to have a causal relationship with this product. An adverse event can therefore be any unfavorable and unintended sign

(including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of the product, whether considered related to the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the product, is also an adverse event.

Symptomatic hypotension and hemoptysis have been defined as adverse events/SAE of special interest and additional documentation is required in the CRF.

The AE may be:

- A new illness
- Worsening of a sign or symptom of the condition under treatment or of a concomitant illness
- An effect of the study medication
- An effect of the comparator drug
- An effect related to off-label use or occupational exposure
- Medication error, overdose, drug abuse, drug misuse or drug dependency itself, as well as any resulting event
- Drug exposure via mother/father (exposure during conception, pregnancy, childbirth and breastfeeding)
- An effect related to lack of drug effect
- An effect related to pre-existing condition improved (unexpected therapeutic benefits are observed)

As mentioned above no causal relationship with a study medication is implied using the term “adverse event”.

9.2.2 Adverse Reaction (AR); also referred to as Adverse Drug Reaction (ADR)

An AE which has a causal relationship with the product, that is, a causal relationship between the product and the adverse event is at least a reasonable possibility. An Adverse Reaction (AR) is any AE judged as having a reasonable suspected causal relationship to Adempas®.

Causal relationship: The assessment of the causal relationship between an AE and the administration of treatment is a clinical decision based on all available information at the time of the completion of the CRF. The assessment is based on the question whether there was a "reasonable causal relationship" to the study treatment in question. Possible answers are "yes" or "no".

An assessment of "no" would include:

- The existence of a clear alternative explanation (e.g. mechanical bleeding at surgical site)
- Non-plausibility (e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration)

An assessment of "yes" indicates that there is a reasonable suspicion that the AE is associated with the use of the study treatment. Factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given The length of time from drug exposure to event should be evaluated in the clinical context of the event
- Recovery on drug discontinuation (de-challenge), recurrence on drug re-introduction (re-challenge): Subject's response after de-challenge or subjects response after re-challenge should be considered in the view of the usual clinical course of the event in question
- Underlying, concomitant, intercurrent diseases: Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have
- Concomitant medication or treatment: The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them may be suspected to cause the event in question
- The pharmacology and pharmacokinetics of the study treatment: The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject’s pharmacodynamics should be considered.

9.2.3 Serious Adverse Event (SAE)/ Serious Adverse Reaction (SAR)

An adverse event or adverse reaction that results in death, is life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, is a congenital anomaly/birth defect, or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered an SAE/SAR when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

An AE is serious (SAE) if it:

- Results in death

- Is life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization (see exceptions below)
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly or birth defect
- Is medically important

Death is usually the outcome of an underlying clinical event that causes it. Hence, it is the cause of death that should be regarded as the SAE. The one exception to this rule is 'sudden death' where no cause has been established. In this instance, 'sudden death' should be regarded as the AE and 'fatal' as its reason for being 'serious'.

Life-threatening: The term "life-threatening" in the definition of "serious" refers to an AE in which the subject was at risk of death at the time of the event. It does not refer to an AE which hypothetically might have caused death if it were more severe.

Hospitalization: Any adverse event leading to hospitalization or prolongation of hospitalization will be automatically considered as Serious, UNLESS at least one of the following exceptions is met:

Hospitalizations will not be regarded as adverse events, if they:

- Were planned before inclusion in the study
- Are ambulant (shorter than 12 hours)
- Are part of the normal treatment or monitoring of the studied disease, i.e. they were not due to a worsening of the disease
- Are required for carrying out a routine right heart catheterization (RHC) procedure for conducting diagnostic invasive hemodynamic measurements to evaluate a patient's underlying disease (without taking into account any clinical suspicion or finding with regard to the worsening of the underlying disease). In this context, a RHC is a procedure and not an adverse event.

However, it should be noted that other invasive procedure or treatment during any hospitalization may fulfill the criteria of 'medically important' and as such may be reportable as a SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedent.

Disability means a substantial disruption of a person's ability to conduct normal life's functions.

Congenital anomaly (birth defect), i.e. any congenital anomaly observed in an infant, or later in a child, should be regarded as a SAE when:

- The mother had been exposed to a medicinal product at any stage during conception or pregnancy or during delivery
- The father was exposed to a medicinal product prior to conception

Other medically important serious event: any adverse event may be considered serious because it may jeopardize the patient and may require intervention to prevent another serious condition. Medically important events either refer to or might be indicative of a serious disease state. Such reports warrant special attention because of their possible association with serious disease state and may lead to more decisive action than reports on other terms.

9.2.4 Non-serious Adverse Reaction (NSAR)

An adverse reaction that does not meet any of the serious criteria in 9.2.3.

9.2.5 Special Situations

The following special situations are considered important safety information and must be reported, regardless of seriousness or causality, if the investigator becomes aware of them:

- Overdose
- Lack of therapeutic effect
- Off-label use, medication error, misuse, abuse, or occupational exposure
- Suspected transmission via a medicinal product of an infectious agent

9.2.6 Sponsor’s Product

Sponsor’s product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

9.2.7 Causality Assessment

A causality assessment is the determination of whether there is at least a reasonable possibility that a product caused the adverse event. Causality must be recorded on the AE form by the investigator for each reported event in relationship to a Sponsor's product.

Primary Data Collection

The assessment of causality is to be determined by an investigator who is a qualified healthcare professional according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product): There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; the AE is more likely explained by the Sponsor's product than by another cause.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

This study will be registered at “www.clinicaltrials.gov" and “www.chinadrugtrials.org.cn”. Results will be disclosed in a publicly available database within the standard timelines.

The results of this study are intended to be published in a peer-reviewed journal and as abstracts/presentations at medical congresses under the oversight of the sponsor. Current guidelines and recommendation on good publication practice will be followed (e.g. GPP2 Guidelines [27], STROBE [28]). No individual investigator may publish on the results of this study, or their own patients, without prior approval from the sponsor.

11 REFERENCES

[1] Galiè et al, ‘Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS),’ *Eur Heart J,* vol. 30, pp. 2493-537, 2009.

[2] McLaughlin et al, ‘ACCF/AHA 2009 expert consensus document on pulmonary hypertension a report of the American College of Cardiology Foundation Task Force on Expert Consensus Documents and the American Heart Association,’ *J Am Coll Cardiol,* vol. 53, pp. 1573-619, 2009.

[3] D'Alonzo GE et al, ‘Survival in patients with primary pulmonary hypertension. Results from a national prospective registry,’ *Intern Med,* vol. 115, p. 343–9, 1991.

[4] Humbert et al, ‘Survival in patients with idiopathic, familial, and anorexigen-associated pulmonary arterial hypertension in the modern management era,’ *Circulation,* vol. 122, p. 156–163, 2010.

[5] Montani et al, ‘Pulmonary arterial hypertension.,’ *Orphanet Journal of Rare Diseases,* vol. 8, p. 97, 2013.

[6] Seferian et al, ‘Therapies for pulmonary arterial hypertension: where are we today, where do we go tomorrow?,’ *Eur Respir Rev,* vol. 22, p. 217–226, 2013.

[7] Benza et al, ‘An evaluation of long-term survival from time of diagnosis in pulmonary arterial hypertension from the REVEAL Registry.,’ *Chest,* vol. 142, pp. 448-56, 2012.

[8] Condliffe et al, ‘Improved outcomes in medically and surgically treated chronic thromboembolic pulmonary hypertension.,’ *Am J Respir Crit Care Med,* vol. 177, 2008.

[9] The NHS Information Centre, 2011. [Online]. Available: https://catalogue.ic.nhs.uk/publications/clinical/heart/nati-pulm-hype-audi-2011/nati-pulm-hype-audi-2011-ref.pdf.

[10] Simonneau et al, 'Updated clinical classification of pulmonary hypertension.,' *J Am Coll Cardiol,* vol. 62, pp. 34-41, 24 December 2013.

[11] Galiè N et al, 'Guidelines for the diagnosis and treatment of pulmonary hypertension: the Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS),' *Eur Heart J,* vol. 30, pp. 2493-537, 2009.

[12] Mayer E; Jenkins D; Lindner J; et al , 'Surgical management and outcome of patients with chronic thromboembolic pulmonary hypertension: results from an interventional prospective registry.,' *J. Thorac Cardiovasc. Surg.,* vol. 141, pp. 702-710, 2011.

[13] Hoeper MM; Mayer E; Simonneau G; et al, 'Chronic thromboembolic pulmonary hypertension.,' *Cirulation,* Bd. 113, pp. 2011-2020, 2006.

[14] Auger WR; Kerr KM; Kim NH; al et; 'Chronic thromboembolic pulmonary hypertension.,' *Cardiol Clin,* vol. 22, p. 453–466., 2004.

[15] Dartevelle P; Fadel E; Mussot S; al et 'Chronic thromboembolic pulmonary hypertension.,' *Eur Respir J,* vol. 23, p. 637–648, 2004.

[16] Pepke-Zaba et al, 'Chronic thromboembolic pulmonary hypertension: role of medical therapy.,' *Eur Respir J,* vol. 41, p. 985–990, 2013.

[17] Grimminger F; Weimann G; Frey R; al et; 'First acute haemodynamic study of soluble guanylate cyclase stimulator riociguat in pulmonary hypertension.,' *Eur Respir,* Bd. 33, pp. 785-92, 2009.

[18] Stasch JP; Pacher P; Evgenov OV, 'Soluble guanylate cyclase as an emerging therapeutic target in cardiopulmonary disease.,' vol. 123, pp. 2263-73, 2011.

[19] Giaid A; Saleh D; 'Reduced expression of endothelial nitric oxide synthase in the lungs of patients with pulmonary hypertension.,' *N Engl J Med,* vol. 333, pp. 214-21, 1995.

[20] Lang M; Kojonazarov B; Tian X; al et; 'The soluble guanylate cyclase stimulator riociguat ameliorates pulmonary hypertension induced by hypoxia and SU5416 in rats.,' *PLoS One,* vol. 7(8), p. e43433, 2012.

[21] Grimminger F; Schermuly RT; Janssen W; Weissmann N; Stasch JP; 'Riociguat for the treatment of pulmonary hypertension,' *Expert Opin Investig Drugs,* vol. 20, pp. 567-76, 2011.

[22] Ghofrani; et al 'Riociguat for the treatment of chronic thromboembolic pulmonary hypertension.,' *N Engl J Med,* vol. 369, pp. 319-29, 2013.

[23] Ghofrani; et al, 'Riociguat for the treatment of chronic thromboembolic pulmonary hypertension.,' *N Engl J Med,* vol. 369, pp. 330-40, 2013.

[24] McGoon; et al, ‘Pulmonary Arterial Hypertension: Epidemiology and Registries.,’ *Journal of the American College of Cardiology*, Bd. 62, 2013.

[25] Humbert M, et al, ‘Survival in incident and prevalent cohorts of patients with pulmonary hypertension,’ *Eur Respir J*, 2011.

[26] ‘ICH Harmonized Tripartite Guideline: Clinical Safety Data Management Definitions and Standards for Expedited Reporting (E2D),’ November 2003.

[27] Graf C; Battisti WP; Bridges D; Bruce-Winkler V; Conaty JM; Ellison JM; Field EA; Gurr JA; Marx ME; Patel M; Sanes-Miller C; Yarker YE; ‘Good publication practice for communicating company sponsored medical research: the GPP2 guidelines,’ *BMJ*, Bd. 339, p. 4330, 2009.

[28] von ELm E; Altman DG; Egger M; Pocock SJ; Gøtzsche PC; Vandenbroucke JP; ‘STROBE-Initiative: The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting of observational studies,’ J Clin Epidemiol, vol. 61(4), pp. 344-9, 2008.

Annex 1 Signatures

Sponsor's Representative

TYPED NAME	SIGNATURE	DATE
_____	_____	_____

Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 9 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

TYPED NAME	SIGNATURE	DATE
_____	_____	_____